PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Management of Asthma in Childhood: Study Protocol of a Systematic Evidence Update by the Pediatric Asthma in Real Life (PeARL) Think Tank.
AUTHORS	Mathioudakis, Alexander; Miligkos, Michael; Boccabella, Cristina; Alimani, Gioulinta; Custovic, Adnan; Deschildre, A.; Ducharme, Francine; Kalayci, Omer; Murray, Clare; Garcia, Antonio; Phipatanakul, Wanda; Price, David; Sheikh, Aziz; Agache, Ioana; Bacharier, Leonard; Beloukas, Apostolos; Bentley, Andrew; Bonini, Matteo; Castro-Rodriguez, Jose A.; De Carlo, Giuseppe; Craig, Timothy; Diamant, Z.; Feleszko, Wojciech; Felton, Tim; Gern, James; Grigg, Jonathan; Hedlin, Gunilla; Hossny, Elham M.; Ierodiakonou, Despo; Jartti, Tuomas; Kaplan, Alan; Lemanske, Robert F.; Le Souëf, Peter; Mäkelä, Mika; Mathioudakis, Georgios; Matricardi, Paolo; Mitrogiorgou, Marina; Morais-Almeida, Mario; Nagaraju, Karthik; Papageorgiou, Effie; Pité, H; Pitrez, Paulo MC; Pohunek, Petr; Roberts, Graham; Tsiligianni, Ioanna; Turner, Stephen; Susanne, Vijverberg; Winders, Tonya A.; Wong, Gary; Xepapadaki, Paraskevi; Zar, Heather; Papadopoulos, Nikolaos

VERSION 1 – REVIEW

REVIEWER	Craig, Simon Monash Medical Centre Clayton, Emergency Department
REVIEW RETURNED	14-Feb-2021

GENERAL COMMENTS	Thank you for the opportunity to review this protocol paper for systematic reviews on acute and long-term management of asthma in children. Overall, the protocol is clearly written. The statement in line 188-192 “other pharmacological interventions that are tested in small trials or real-life studies, often showing promising results…” is probably a little strong… The references provided include case reports, review articles of pre-clinical work (VIP agonists), and don’t really make a compelling case for including these other, non-established therapies. Have the authors pre-specified age groups or asthma phenotypes of interest? With regards to the systematic review of clinical studies evaluating the management of acute asthma attacks, the authors refer to a two-stage approach, firstly using a broad strategy to identify all pharmacological treatments, and secondly to find “medications that showed positive clinical results, but are not yet recommended by clinical practice guidelines” (line 258-260)

	Which clinical practice guidelines will be used to determine whether a treatment is recommended or not? What if the guidelines do not agree (there are varying recommendations of IV aminophylline and IV salbutamol in particular)? If a treatment is already recommended, will a further detailed systematic review be performed? Or only if a treatment is NOT recommended? Many guidelines have statements along the lines of "consider in consultation with ICU" – for the purposes of deciding whether or not the medication is included in the systematic review, how will medications with some sort of qualifier / "consider" statement be handled? It may be worth explicitly stating which guidelines you will use to determine whether or not a particular treatment is recommended or not, and how this will be decided. The time course for an acute asthma exacerbation is usually quite short – symptoms come on rapidly and often resolve within a few days with appropriate treatment. Most authorities recommend a course of steroids for 3-5 days. In light of this, please justify the choice of two weeks for the primary outcome and 6 months for secondary outcomes. The definition of "treatment success" is clear, but possibly not particularly useful. Outcome measures used in asthma trials are very heterogenous, and success in one trial may be an improvement in an asthma bedside score (eg PRAM score, PAS score), while in another it may be avoidance of intubation. These are not particularly comparable. Line 417 – with regards to the later – should be "latter" As the study describes an interest in acute asthma presentations requiring emergency department attendance +/- hospital admission, it may be worth amending the search strategy (presented in the online appendix) to include terms relating to the emergency department, as well as intensive care / critical care.

REVIEWER	Ali, Mohammad Mohammed Al-Mana College for Medical Sciences, Pharmacy
REVIEW RETURNED	13-Mar-2021

GENERAL COMMENTS	Title: Management of Asthma in Childhood: Study Protocol of a Systematic Evidence Update by the Pediatric Asthma in Real Life (PeARL) Think Tank. I take this opportunity to thank the journal editor for giving me an opportunity to review this manuscript. The manuscript addresses an important aspect of Management of Asthma in Childhood. However, the manuscript may accepted after following minor correction. As per Journal manuscript writing guideline kindly change followings. In Abstract: Kindly remove Colon character (:) from Introduction: make change as Introduction and so on Methods and analysis: Ethics and dissemination: Systematic review registration:

	Kindly arrange reference as per journal latest author's instruction for manuscript writing.

REVIEWER	Boechat, Jose Universidade Federal Fluminense, Internal Medicine
REVIEW RETURNED	17-Mar-2021

GENERAL COMMENTS	It is an interesting and very welcome study protocol, with the aim to develop evidence updates on childhood asthma treatment (maintenance and acute attacks), generating data that can be used to guide future research. Below, I describe some doubts and specific suggestions to be considered by the authors. Lines 128-136: Possible limitations of the protocol are not described. What limitations do the authors expect to encounter in the implementation of this study protocol? Line 138: Keywords. I suggest including: "asthma maintenance treatment" and "acute asthma attacks treatment" Lines 292-293: Why here (SR of clinical studies evaluating the management of acute severe asthma attacks) there is no language restrictions, differently from what has been described to maintenance pharmacotherapy (line 205)? Lines 308-309: Why EMBASE is searched here, and not for maintenance pharmacotherapy (line 215)? Lines 390-393: I consider very relevant that the opinion of patients and their caregivers has been taken into account in the selection of priorities in any research. Please, describe in a little more detail the weight of the expectations of patients, caregivers and patient organizations in the process of organizing this research protocol. Will the opinion of this lay public also be taken into account when the research results are released?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Simon Craig, Monash Medical Centre Clayton

Comments to the Author:

Thank you for the opportunity to review this protocol paper for systematic reviews on acute and long-term management of asthma in children.

Overall, the protocol is clearly written.

The statement in line 188-192 "other pharmacological interventions that are tested in small trials or real-life studies, often showing promising results…" is probably a little strong… The references provided include case reports, review articles of pre-clinical work (VIP agonists), and don't really make a compelling case for including these other, non-established therapies.

Response: We would like to thank Dr Craig for the thorough peer review and productive comments. We have now toned down this sentence as suggested and we have also replaced the references in question with more appropriate references. “However, when evaluating the literature, we identified several other pharmacological interventions that are tested in small trials or real-life studies, and while they may show promising early results, they have not been assessed further or introduced in clinical practice guidelines”.

Have the authors pre-specified age groups or asthma phenotypes of interest?

Response: We have not. We will accept any age groups and asthma phenotypes described. The body of evidence regarding age groups or specific asthma phenotypes is already thin, for most evaluated interventions and we would not like to end up having to exclude studies from these subgroup analyses due to a very strict protocol.

With regards to the systematic review of clinical studies evaluating the management of acute asthma attacks, the authors refer to a two-stage approach, firstly using a broad strategy to identify all pharmacological treatments, and secondly to find “medications that showed positive clinical results, but are not yet recommended by clinical practice guidelines” (line 258-260)

Which clinical practice guidelines will be used to determine whether a treatment is recommended or not? What if the guidelines do not agree (there are varying recommendations of IV aminophylline and IV salbutamol in particular)? If a treatment is already recommended, will a further detailed systematic review be performed? Or only if a treatment is NOT recommended?

Response: The aim of these focused systematic reviews is to explore promising, but not yet established treatments. So, we will not perform systematic reviews for treatments that are thoroughly evaluated, and we know that they work [or that they do not work]; as these are frequently addressed by Cochrane Airways, guideline panels and other groups. We have clarified in the manuscript that our aim is to identify interventions that are not yet recommended, but could possibly be considered for use in clinical practice, or might require further evaluation in clinical research studies to confirm their safety and effectiveness profiles: “Next, medications that showed positive clinical results, but are not yet thoroughly evaluated in clinical studies and meta-analyses and are therefore not recommended by international asthma guidelines (such as the National Institute for Health and Care Excellence [NICE] asthma guidelines, the British Thoracic Society and Scottish Intercollegiate Guidelines Network [BTS/SIGN] asthma guidelines, the National Asthma Education and Prevention Program [NAEPP], or the Global Strategy for Asthma Management and Prevention [GINA] document), will be selected and further evaluated in individual meta-analyses. The aim will be to identify novel interventions that

could be recommended for use in clinical practice, or might require further evaluation in clinical research studies, to confirm their safety and effectiveness profiles."

Many guidelines have statements along the lines of "consider in consultation with ICU" – for the purposes of deciding whether or not the medication is included in the systematic review, how will medications with some sort of qualifier / "consider" statement be handled?

Response: Please see our previous response. The aim of the individual meta-analyses is to look for novel interventions that have only been preliminary evaluated with promising results but are not yet considered in guidelines. We do not intend to update all systematic reviews that lead to conditional recommendations as our planned work is already extensive, and we need to safeguard the feasibility of completing the proposed research work. This has already been clarified through our previous response.

It may be worth explicitly stating which guidelines you will use to determine whether or not a particular treatment is recommended or not, and how this will be decided.

Response: Thank you. We have clarified that we will use any of the main clinical practice guidelines addressing acute attacks, available in the English language (NICE, BTS/SIGN, NAEPP, GINA or others).

The time course for an acute asthma exacerbation is usually quite short – symptoms come on rapidly and often resolve within a few days with appropriate treatment. Most authorities recommend a course of steroids for 3-5 days. In light of this, please justify the choice of two weeks for the primary outcome and 6 months for secondary outcomes.

Response: Thank you for pointing this out. We have now further clarified: "Treatment success or treatment failure rate evaluated at any timepoint, within 2 weeks from presentation". We chose to accept treatment success or failure evaluated at any point within 2 weeks from presentation, as we would not want to exclude studies that have evaluated treatment success or failure slightly later. Timepoints of outcomes assessment will be reported transparently to facilitate readability and interpretability of the final report.

The definition of "treatment success" is clear, but possibly not particularly useful. Outcome measures used in asthma trials are very heterogenous, and success in one trial may be an improvement in an asthma bedside score (eg PRAM score, PAS score), while in another it may be avoidance of intubation. These are not particularly comparable.

Response: We agree that clinical studies evaluating therapeutic interventions for acute asthma (including acute asthma in children) report on heterogeneous outcomes. A core outcome set would definitely improve the quality and comparability of RCTs. Unfortunately, in the meantime we should make the best use of the available evidence. We fully intend to report transparently the definitions of treatment success across the included studies. We have now clarified that meta-analyses will be conducted when it will be considered meaningful. We accept this is not an ideal definition for the protocol, but it is a pragmatic one. Actually, this is the suggested phrasing in the Cochrane Airways SR protocol template. We hope this will be acceptable. "The definitions of treatment success and treatment failure vary significantly across clinical studies evaluating the management of acute asthma in children; for this reason, meta-analyses will only be conducted in cases they are considered meaningful by the investigators".

Line 417 – with regards to the later – should be "latter"

Response: Done.

As the study describes an interest in acute asthma presentations requiring emergency department attendance +/- hospital admission, it may be worth amending the search strategy (presented in the online appendix) to include terms relating to the emergency department, as well as intensive care / critical care.

Response: Thanks – Done.

Reviewer: 2

Dr. Mohammad Ali, Mohammed Al-Mana College for Medical Sciences

Comments to the Author:

Title: Management of Asthma in Childhood: Study Protocol of a Systematic Evidence Update by the Pediatric Asthma in Real Life (PeARL) Think Tank.

I take this opportunity to thank the journal editor for giving me an opportunity to review this manuscript. The manuscript addresses an important aspect of Management of Asthma in Childhood. However, the manuscript may accepted after following minor correction.

As per Journal manuscript writing guideline kindly change followings.

In Abstract:

Kindly remove Colon character (:) from

Introduction: make change as Introduction and so on

Methods and analysis:

Ethics and dissemination:

Systematic review registration:

> **Response:** We would like to thank Dr. Ali for the helpful comments. We have now removed the colon characters, as advised.

Kindly arrange reference as per journal latest author's instruction for manuscript writing.

> **Response:** We can confirm that the references are arranged as per the journal's author instructions.

Reviewer: 3

Dr. Jose Boechat, Universidade Federal Fluminense

Comments to the Author:

It is an interesting and very welcome study protocol, with the aim to develop evidence updates on childhood asthma treatment (maintenance and acute attacks), generating data that can be used to guide future research.

Below, I describe some doubts and specific suggestions to be considered by the authors.

Lines 128-136: Possible limitations of the protocol are not described. What limitations do the authors expect to encounter in the implementation of this study protocol?

> **Response:** We would like to thank Dr. Boechat for the productive comments. A potential limitation of our overview of systematic reviews is that we may not be able to capture adequate data regarding the differential effectiveness of interventions across different patient groups (planned subgroup analyses). We have clarified that both in the Strengths and limitations section of the abstract and the discussion:
>
> Strengths and limitations: "A potential limitation of the overview of SRs is that the feasibility of conducting the planned subgroup analyses will depend on whether relevant data have been captured in existing SRs".

Discussion: “A potential limitation of this approach is that we might not be able to capture adequate data regarding the differential effectiveness of interventions across different severity groups, age groups, or pediatric asthma phenotypes, if these have not been captured in existing SRs. Moreover, existing SRs may not capture some of the most recent studies, that may have been published after the SRs, although preliminary searches have revealed several very recently update meta-analyses.”.

Line 138: Keywords. I suggest including: “asthma maintenance treatment” and “acute asthma attacks treatment”

Response: Done

Lines 292-293: Why here (SR of clinical studies evaluating the management of acute severe asthma attacks) there is no language restrictions, differently from what has been described to maintenance pharmacotherapy (line 205)?

Response: Thank you for highlighting this issue. We have clarified that all our systematic reviews will only consider studies reported in the English language, as we anticipate to include a large number of studies and we do not have the resources required for translation of studies published in other languages, at present.

Lines 308-309: Why EMBASE is searched here, and not for maintenance pharmacotherapy (line 215)?

Response: For maintenance pharmacotherapy, we will conduct an overview of systematic reviews, and therefore, we will only include systematic reviews. However, systematic reviews from EMBASE are already included in the Cochrane Library. On the other hand, for acute attacks, we intend to evaluate original studies (both randomized controlled trials and real-life studies). While the RCTs from EMBASE are also included in the Cochrane Library, the same is not true for real-life studies. For this reason, we chose to search EMBASE as well for this systematic review, for completeness.

Lines 390-393: I consider very relevant that the opinion of patients and their caregivers has been taken into account in the selection of priorities in any research. Please, describe in a little more detail the weight of the expectations of patients, caregivers and patient organizations in the process of organizing this research protocol. Will the opinion of this lay public also be taken into account when the research results are released?

Response: Thank you for this comment. Actually, a patient representative (TW) has joined our research group, provided input in this study protocol and will also provide input throughout the study process. Moreover, plain English summaries of the final reports will be developed and shared with relevant patient organisations. We have also explored the literature for a relevant core outcome set or studies evaluating the preference of patients with childhood asthma regarding outcome measures, but we were not able to find any relevant data to inform the selection of outcomes for our review.

We have now clarified these in the manuscript: “Plain English summaries of the final reports will be developed and shared with relevant patient organisations” and “Moreover, a patient representative (TAW) has joined the research group and provided input in this study protocol and she will also provide input throughout the study process”.

VERSION 2 – REVIEW

REVIEWER	Craig, Simon Monash Medical Centre Clayton, Emergency Department
REVIEW RETURNED	27-May-2021

GENERAL COMMENTS	Thank you for submitting a revised manuscript. I am happy to recommend for publication.

REVIEWER	Boechat, Jose Universidade Federal Fluminense, Internal Medicine
REVIEW RETURNED	29-May-2021

GENERAL COMMENTS	I thank the authors for their answers to the reviewers' questions, which greatly enriched the research protocol. I hope to be able to read the results of this endeavor soon.